DRUG INFORMATION ASSOCIATION

FDA/DIA SCIENTIFIC WORKSHOP ON FOLLOW-ON PROTEIN PHARMACEUTICALS

BREAKOUT SESSION A:

PHYSICAL CHEMICAL CHARACTERIZATION & IMPURITIES

Monday, February 14, 2005

1:32 p.m.

Marriott Crystal Gateway
1700 Jefferson Davis Highway
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M O D E R A T O R S

BARRY CHERNEY, PhD [CHAIR]

STEPHEN MOORE, PhD, CDER/FDA

ANDREW CHANG, PhD, CBER/FDA

CHARLES DILIBERTI, PhD

REED HARRIS, PhD

P R O C E E D I N G S

DR. CHERNEY: Okay. I think we have a very tight schedule, a lot of information, a lot of discussion we'd like to have. So I think we'd like to start this breakout session.

I want to welcome everybody to the Breakout Session A on "Physical Chemical Characterization and Impurities." I think this is a critical topic when you're talking about follow-on biologics. The physical chemical characterization is going to be the foundation of any similarity exercise that you perform.

So I'd like to start by introducing the moderators. My name is Barry Cherney. I am the Deputy Director of the Division of Therapeutic Proteins in CDER. And I'll let the other panel members introduce themselves.

DR. HARRIS: I'm Reed Harris. I'm with Analytical Development at Genentech.

DR. MOORE: I'm Stephen Moore. I'm a Chemistry Team Leader in CDER, Office of New Drug Chemistry.

DR. DILIBERTI: Charlie Diliberti, Vice President, Scientific Affairs, at Barr Laboratories.

DR. CHANG: Andrew Chang, Acting Division Director, Division of Hematology, Office of Blood, CBER/FDA.

DR. CHERNEY: Thank you. I wanted to start this session by talking a little bit about the format of the session, and then some of the ground rules that we have for the session. First, that there are three moderators for the session: the FDA; the innovator, represented by Reed Harris; and then the follow-on manufacturer, represented by Charlie Diliberti.

FDA will be charting the discussion on the chart, and that will be done for this session by Steve Moore. And then we'll be also taking notes in addition to the official transcriber that you can see here in front of me.

The FDA moderator is going to be presenting the questions. And the industry moderators will then provide a point-counterpoint

to the question; followed then by opening up the discussion with the audience. Each question--and we have a series of three--will be followed sequentially. So we'll do the first question, then the second, then the third.

Important issues and points will be identified and recorded, including both where consensus is reached and where we haven't reached consensus. And we've also thought that if there are important points but they're not really on-topic, that we'll put them into sort of a parking space.

There's going to be a time limit for the three questions; and we think that 15, 30, and 40 minutes, sort of reflecting the complexity of the issues. And of course, the moderators may be asking more specific questions to focus the discussion during the discussion.

Now, the ground rule, as you've heard probably, is that speakers should speak from a microphone and identify themselves and their affiliation. The statements are going to be

reviewed and will represent individual opinions, and not those of a particular organization, unless you so state. I think this is important, particularly for the FDA where, whenever somebody from the FDA speaks, everybody thinks that they're representing the FDA. Here it's personal opinions. I think that will stimulate the discussion of people to express their opinions.

The focus should be on the scientific issues, and not the legal or regulatory. Sometimes you might on the scientific issue cross the boundary of what is currently legal or not. I think in some circumstances that's okay; but we're only talking science, and not the legal issues.

The discussion should focus on the physical chemical attributes and characterization studies; not biological activity, not immunogenicity. Those will be covered in others. Now, of course, you're going to have to reference some of those things, but we won't have a long discussion on the merits biological activities.

And of course, we'd like to talk about

protein products that have significant tertiary and quaternary structure, and should start from the more simple to the more complex situations. Now, even for a glucagon with a 30 amino acid peptide, there is tertiary and certainly quaternary structure. So all those types of products we can be talking about.

The persons from the audience should speak for about two minutes to the issue. There are going to be questions perhaps that the moderators may ask to sort of elucidate what the speaker is saying, and the audience may also have some questions for the speakers.

And what we'd like to do is when we're having a discussion on a particular topic, to let that topic run its course or the issue to run its course. So that means if you're lined up for talking on the microphone out in the audience and there's a specific topic, we'd prefer that you don't change topics, but let somebody who has a counterpoint to a point that was made speak, and then we can move on to another issue. So we'd like

to try if we can to complete the discussion on the one issue before we move to the other.

And of course, finally, the discussion should be data-driven. Hard copies of the data and references should be submitted to the docket. And I provide a docket number up here where you can submit that information.

And then, the first question that we'd like to talk about is: Which Product Attributes Should Be Evaluated? Now, the product attributes are going to be the molecular characteristics of the active pharmaceutical ingredients, as well as the other constituents of the drug product. Now, these are going to describe the identity, purity, potency, safety from avaticious [ph] agents, stability of the molecule, impurities, all those things. But we'd like to focus on things that are important for the product attributes, that are important for a similarity exercise.

The other thing is that when we're talking about evaluating in this question, we're talking about what physical or what product attributes

should you monitor and analytically either quantitatively or qualitatively analyze.

So with that, I will turn to the first point, by Reed Harris.

DR. HARRIS: All right, thanks, Barry. I'm Reed Harris. I've been with Genentech for 21 years. And virtually every product that we've brought through clinical development or commercialization has gone through my lab at some point. And I can assure you that every sine one of them has presented us with some unwelcome surprises.

This morning Keith asked if we could talk about less complex or more complex proteins. And I have to say that even if you go back to the growth hormone literature, you'll see that there were a lot of complex issues that had to be dealt with, even for an apparently simple molecule. So despite the great confidence that we have in our analytical abilities and in our process development abilities, we still get surprised and are occasionally humbled by what happens.

So one of the things that we need to do is to establish what's known about the molecular characteristics that mediate, for example,

bioavailability, or potency, or safety; and in particular, looking at those attributes that may trigger immunogenicity.

In addition, we take a look at the routes of degradation. This helps us to establish end-process hold times and to establish stability indicating methods so that we can do product expirations.

And then we also, of course, need to take a look at the effects of the container that different containers may have. Leachates could get into the product and those themselves could trigger new issues, either by serving as an adjuvant, or by activating a protease, or perhaps even modifying the protein.

And then the other issue that I have listed there in the process of related impurities is wholesale proteins. There's a tremendous amount of investment that is needed to generate

appropriate wholesale protein assays using the right reagents from the right cell lines. And that's one of the issues that I think we'll be challenging as we go forward, is how to compare the wholesale protein assays that are generated for different products by different manufacturers.

DR. CHERNEY: The next one will be the counterpoint, with Charles Diliberti.

DR. DILIBERTI: Thanks, Barry. Which product attributes should be evaluated? In a nutshell, all of them. Whether it's a first manufacture for a particular product or a second manufacture, all proteins need to be well characterized.

We need to keep in mind, though, that this characterization is a comparative one; a side-by-side analysis of the two products. This is not a situation involving a prediction of safety or toxicological or pharmacological properties from physical chemical properties in a new chemical entity de novo. This is a side-by-side comparison.

And we need to use the full array of

analytical tools at our disposal. As we heard this morning, it's clear that over the past couple of decades the analytical tools have increased both in the number of tools available and their tremendous power. And we need to use all reasonable analytical tools to achieve this goal.

The next issue is that we need to perform, as we heard this morning, multiple redundant measures using a variety of analytical tools. The key concept here is that the tools need to be orthogonal. They need to be independent measurements of independent physical properties; not just themes and variations on a particular analytical method.

The characterization obviously needs to address the identity, purity, and potency of the product. And finally, the results from any given test should not be viewed in isolation but, as also we heard this morning, they need to be viewed collectively across all tests, to develop a highly sensitive and selective fingerprint of the two products being compared. Thank you.

DR. CHERNEY: Okay. Well, I think we have one answer to this question already, in terms of which product attributes should be evaluated. And

that is that it seems to be that all should be fully characterized and evaluated.

Is there anybody who would think that you need only a subset of the product attributes? Okay. So we reached, actually, consensus. And this probably will be the first time today that we will have--probably the first and last time.

[Laughter.]

DR. CHERNEY: But I think there are other things to ask about. When you're talking about orthogonal methods, how much is enough in a method? How many orthogonal methods do you use? There are multiple methods for looking at aggregate. You can use ten or 15 types of methods. How many are you going to have to look at before you have a sense of the aggregation state?

Should we test to infinity, that we should say for each attribute you should be testing as much as you can, as much is available? Do you use

all available assays? Or are we going to be selective? What does the relevant assay or comparative assay mean?

DR. CHAMBERLAIN [In Audience]: Paul Chamberlain, MDS Pharma Services.

I guess what I'm worried about in what I've heard today is really a lack of focus based on what we know from substantial experience now about structural activity relationships for most of the products we're talking about. So in terms of this suggestion that we would test effectively to infinity just in case there are some surprises, is to me not a scientifically valid position.

And in particular, we could look at the complex case of Eprex [ph] epoetin, where we know and where it's been documented very clearly that the major determinant for both its in vitro and in vivo biologic activity is the degree of tetra and ternary sylated glycones. So we have some very strong clues about where to focus our evaluation.

Similarly for GCSF, we know that often there are a thousand and one ways of isolating that

protein from inclusion bodies. Equally, we know that we can measure using fairly standard techniques now oxidation variants that could be important to both the safety and the potency of the molecule. Therefore, I think we can be guided, and we should be guided, by what is available in the database.

DR. CHANG: Before you sit down, can I ask a question? Now, I'm not sure of the nature of your company and whether it's an innovative company or a follow-on protein or genetic company. Now, when you said that in some of the knowledge of the functional structure relationship we should focus on those things that you deem is important, can you share with the audience how do you learn those critical aspects of the product? Is that from your own process, from your own development? Or do you learn from other means? Thank you.

DR. CHAMBERLAIN [In Audience]: Okay. The data is available substantially in the public arena via two collaborative studies which have been sponsored by the European Department of Quality of

Medicines and run out of MIBSC, amongst other organizations, and data published by Patrick Storing and Associates which clearly demonstrates the major determining factors of both the in vitro and the in vivo activity of these molecules. Does that answer the question?

DR. CHANG: Yes, that helps. Thank you.

DR. SHRIVER [In Audience]: Zach Shriver, Momenta Pharmaceuticals.

I guess the point I'd like to bring up is that orthogonal techniques--My take on it is orthogonal techniques in using multiple physical and chemical characterization tools doesn't necessarily mean using an infinity of techniques. Rather, through integration of techniques it's possible to understand the structure and potentially the function of biologics. And through integration of techniques you really strengthen the overall data set. You aren't limited by the strengths or failings of one particular technique. But rather, through integration you get a complete picture.

DR. CHERNEY: I'd like to follow up on what we're talking about, in terms of using literature and scientific studies that have been

published in the literature. And, yes, you might find a study that says the importance of glycosylation in terms of biological activity, both in vitro and in vivo. But there are a lot of other things that can occur to molecules--oxidation, deamidation, truncation--there's a lot of things that occur with molecules that you don't necessarily know; and may actually affect the potency, may affect biodistribution, may affect immunogenicity. And those are all unknowns about product attributes.

So the question is: Can you really rely totally on literature for these things, or are there other things?

MS. NOVAK [In Audience]: Jeanne Novak, CBR International.

I think with regards to relying solely on the literature, I don't know that anyone here would say that that's the end-all and be-all. I think we

know that obviously there are going to be only subsets of data that are presented, not only for a particular technique, but certainly with regards to full characterization.

I think the statement to perform all available--or use all available tools is also a bit overstated; in that not everyone may have access or, for example, require access to circular dichroism [ph], for example. You might have another battery or subset of techniques just as powerful if you're looking at, for example, mass spec evaluations of a protein, depending on how you utilize that and what you're looking for. And also, how you prepare, for example, the particular not only API but maybe precursors to the API or intermediates in the manufacturing process, I think, also has to be considered.

But the point is if one just throws a battery of tests, everything that you can think of, at the molecule, I think one of the problems one runs into is then you generate a lot of data which isn't necessarily thought out with regards to

priority.

So I agree you have to have an integrated approach, but I think you have to have a priority, knowing exactly what it is you do want to hone in on. And I think that was what was brought out by the previous person commenting from MDS.

So I just wanted to put that out there, as well. Because you certainly can lose a lot of the detail and the sensitivity by just throwing everything out. I think you have to do the best characterization and prioritize it, and I think there are several examples of that. And I'll step aside for a minute.

MS. ZHU [In Audience]: Yes, I'm Rong-Rong Zhu, from Abbott Bio Research.

And actually, I also have a question about fully characterized biopharmaceuticals. Maybe the technology right now is still limited. And one example is probably most people working on the monoclonal antibody characterization. And if you do use the orthogonal technique, like [inaudible] change and CIEF, and if you combine those two

technologies, they do have correlation, but they don't exactly match.

And also, if you try to characterize every single acidic [ph] peak in the ion change chromatogram you actually cannot get a quantitative match of all the deamidation or any other [inaudible] modifications.

So the question is maybe ten years down the road we'll have all the technology. At this time, we may not be able to 100 percent characterize every single piece you see on the chromatogram and its bioactivity assay enough to prove this drug. Even the things we are not able to 100 percent characterize, they're still able to prove to be made drugs on the market.

DR. CHERNEY: Thank you.

MR. POLASTRI [In Audience]: Gian Polastri, Genentech.

I have a question to the panel, or anyone else in the audience who would like to address it. When we speak about full characterization or all attributes should be tested, I guess it presumes

that you know what to look for. Because otherwise, the best of assays are really only designed to look for specific things, and you may well miss things, depending on how you design your analytical approach. So that's the first question.

Then secondly, that's only half the question, anyway. Because once you do the limited characterization or want to be full characterization, it's not likely you're going to come up with identity, and you still then are faced with having to decide which subtle differences between your two comparison molecules are going to be significant or not. And how you go about ascribing relevance to those differences, I think you're back into the same boat that the innovator was in, to relate those differences to a clinical experience of some kind.

And the third point I'd like to put out is some of the specific examples I think I can cite in terms of things that you would miss unless you knew what to look for might be things related to the impurities that come from the process that are not

detectable in the final product because of the limitations, the limits of detection of the particular assay that might be used, if you have an assay that would be capable of seeing it, but you only see it further upstream. That doesn't mean those impurities are not there; they're just below detectable limits. Or secondly, some things that might be associated with the product, but otherwise would be unanticipated, but are a unique attribute of the process by which the product was made, not inherent in the molecule itself.

DR. CHERNEY: Well, I think you make a good point. And actually, one of the lessons that we learn from comparability studies is that you sometimes don't see what you're not looking for. So even though manufacturers may use robust characterization studies, if you have an oxidation and you're not looking particularly for that, your procedures, even though you're using all the correct procedures--you're using peptide mapping and various other procedures to look at the oxidation, veristase [ph], APLC--all those things

may miss it because the procedures haven't been resolved or are capable of resolving those molecules.

So one of the things is how do we mitigate the risk that undetected differences in product attributes are actually present, but you're not detecting? Do you go and validate each assay so that you show that it's capable of detecting each oxidized species that could potentially be present? How do we mitigate that risk? We've heard about literature mitigating some of that risk by identifying what can happen. come on up.

DR. NAKTINIS [In Audience]: Hello, everyone. Vytautas Naktinis, Probios Consulting, but working for Teva Pharmaceuticals.

Actually, my answer to the question which was right now raised in the audience would be the same as the previous one. How much we have to characterize and be confident that the risks are minimized. So the answer, and also how do we look for the things which we don't know that we have to with it?

One has to keep in mind that no genetic manufacturer develops a genetic product in a vacuum, in the absence of previous knowledge, in

the absence of public knowledge. That's one point.

Second, to develop even follow-on product, you have to go through the full development phase, which already was told today with respect to CMC section. So this is a lengthy process, and during that you accumulate an enormous database which allows you to navigate through the problems.

There is a third point. You have the innovator's product in your hands. And you have not one batch; as everyone knows already, you have numerous batches, because you do development over the years. So you have access essentially to numerous batches. So you test variability and you learn. Each little tiny peak, you investigate, and you see if your product is within the limits, or whatever, in the range, of both impurities or other forms which the innovator has demonstrated as safe. That means you are safe.

And I believe that this particular

statement allows us to get out of this black box and just start thinking logically; putting the target, answering the target; putting the question, answering the question. Thanks.

DR. HARRIS: Yes, so let me ask a different question, then. If you got the same analytical profile as the innovator's material, do you need to reassign the characteristics of those peaks and define them anew as product-related impurities or not? Or can you just say, "The pattern matches, and therefore these are similar"?

DR. NAKTINIS [In Audience]: There will be no universal answer. You have to look again, product for product and isoform for isoform. And again, you will rely on literature. And you know which particular modifications could be harmful, you know which are irrelevant at least.

And again, if you are within the limit--Or usually, to my experience and the experience of the company I work for, usually the follow-on product is much more pure, much more homogeneous, than the original product. So in fact, we are speaking a

little bit the reverse situation.

DR. CHERNEY: I just want to pose one question. I hear the innovators talk about all the developmental history, all the knowledge of the product they have during clinical trials, during development. Now, that would appear to me to be more extensive than follow-on manufacturing because the innovator has been at it for 12, 15 years--maybe two decades of information. They're likely to have more information, as they state they have, a lot more information; understand their product to a higher level.

A lot of that information may not be public knowledge; although the FDA may have access to that and know that. But none of that is going to be in the hands of the innovator, and none of that data is legally accessible for any comparer. So how can we mitigate that risk that there actually are product differences that everybody is aware of but nobody can actually look at and see? And is it true that innovators do have extensive data that may not be available for other people?

DR. CHAMBERLAIN [In Audience]: Yes, Barry, to partly address that, and also to come back to the point that Reed was making very well,

Linda Woodle [ph] has said very publicly that for GCSF--which we've got a huge amount of experience on now--Amgen did make changes in the way they isolated that molecule.

They continue to develop their analytical technology. They continue to identify new product-related variants. And yet, the finished product specification, to my knowledge, never changed once in over ten years, and it didn't impact on the safety or efficacy profile of the product.

So it is quite possible that a follow-on manufacturer, because of the improvement in analytical technologies, might detect different product-related variants. But that doesn't necessarily make that a risk factor. That has to be qualified by appropriate supporting studies, maybe in the pre-clinical environment.

DR. CHERNEY: I think at this point we

have to move on to the second question. But thanks for the discussion. So the second question is: What are the capabilities and limitations of the available analytical tools to evaluate those identified product attributes?

Now, I think most people would say that the complete or absolute chemical identity, structure of a small molecule is the norm. However, for the protein entities that we're dealing with, you can't get the complete or absolute molecule-by-molecule, atom-by-atom description of the molecule. So the question is, what are those capabilities and limitations?

And while we didn't identify it, I think there are certain parameters of product attributes that we should be concentrating on perhaps, like identity, purity, impurities, potency of the product, all those things. So in terms of those things, what are the limits of these capabilities?

And again, if we speak to these things, we should try it from the least complex to the most complex. But first, we'll turn back to Reed

Harris.

DR. HARRIS: Okay. So what are the capabilities and limitations of the analytical tools to evaluate important product attributes? Clearly, the limits are a function of the size of the molecule, the number and the site and the nature of the modifications that are present, and also the number of polypeptides that are found.

What we're finding, for example, with the monoclonal antibodies is that you only need one modification site anywhere in one chain, and it shifts it to an evolution position. And it's really hard to figure out what's different about this form, because you have to analyze the alternate form against the background of the normal form, if you will. And so that's one of the issues that we're constantly dealing with.

Another is there are differences when you're looking for a single modification that's present across a large number of sites. An example of that would be glycation. We see this in some of our products in the range of a half a percent

distributed over ten or 20 sites. You would never see that in a peptide map, but you can see it when you analyze the intact protein.

Conversely, though, if you have site-specific modifications, like oscillation, a lot of times you can identify those by looking at peptide maps, rather than looking at the protein as a whole.

So you have to tailor the analytical methods to answer the question that you're trying to get to and, you know, always bearing in mind that you're going to create some blind spots as you go along.

One of the other issues that we've come up with, of course, is glycosylation. And that was discussed--I'm sorry, I wanted to talk about deamidation first. We have really good tools for monitoring deamidation, but right now what we're finding, again with the antibodies, is that we have a lot of acidic forms that in the structures we haven't been able to completely define. So we can assign some of the acidic character, but not all of

it.

And when we get in that situation, then we do have to fall back on the fact that we're using the same cell line and the same manufacturing process and the same analytical methods as we go through process changes and post-approval changes.

The other thing that's an issue for us is aspartate isomerization. And this one is particularly nettlesome because when aspartate changes to isoaspartate it shifts the charge orientation, and often it completely wipes out potency. And this is the type of change that's really hard to detect, because it doesn't change the charge and it doesn't change the mass. And so a lot of the techniques that were discussed earlier today simply won't affect it.

Like oscillation, there was a lot of discussion this morning about the analytical abilities to generate data; again, how you use that data to make decisions about what's important. We have molecules for site occupancy. That's critical for activity. We have other molecules; for

example, the linercept [ph] example that was discussed at the September meeting, where the terminal carbohydrate groups mediate clearance. And so in that molecule you'd probably want to look at a different characteristic.

And then certainly those of you who are working with cytotoxic antibodies probably were caught a little bit surprised by the fact that it's not terminal galactose [ph] and some of the easy carbohydrates that you can monitor that affect cytotoxicity; but it looks now like more and more that the presence or absence of fucose is important. And who would have thought that a few years ago?

So you have to do a wide range of analytical techniques. That's the first part. But really, the second step is critical. And so for us it's kind of an iterative process, where we start with a predicted structure, we look for the usual modifications, and then we spend a lot of time looking at the contrary data because that's where the really interesting stories are. And that's

where the find the variants and the anomalies that sometimes cause us to go back and start over again with respect to cell line or recovery process development.

DR. DILIBERTI: Thanks, Reed. Well, I think it's important to know that complete comparative characterization is both possible and routine for most protein products. This is not a new branch of science that we're creating. It's used routinely in the context of supporting manufacturing process changes, and it's the basis for really product comparisons.

And I think the same logic, the same criteria need to be applied to the issue of comparisons between manufacturers, between products from different manufacturers. Modern analytical tools are capable of elucidating full covalent structures. They are also sensitive to detecting differences in higher order structure, in fingerprinting. And we also have very sensitive methods for measuring impurities.

And if there are situations where it is

believed that the analytical tools are incapable of detecting changes that might be clinically meaningful, then we have to rethink the whole issue of how we make process changes. But I think that that is not really the valid concern here. Thank you.

DR. CHERNEY: Okay. As you're getting to the microphone, I did want to make one announcement. It is that our transcriber would like everybody who actually does make a statement that they should come to see her and spell their name or give her a business card, so that she can accurately represent who was speaking. Thank you.

DR. FISCHER [In Audience]: My name is Stephan Fischer, from Roche [inaudible] in Germany.

If I read that statement, complete comparative characterization, if you refer "complete" to doing all these methods and then collect data, that's just a part of it. And what I miss in this discussion is that if we do that in the industry, we do that in the context of everything else we do.

So my understanding is that we use these methods through process validation, in process controls. We can establish hypotheses to exclude

that certain events happen. And having that confidence that we understand that, we can have a reasonable interpretation of the data that we generate through these methods.

So for me, it's difficult to take that message without the context of process development and validation, and simply look at the analytical methods and interpret the data as they are just from characterization.

DR. CHERNEY: Can you give us an example where that lack of information was detrimental to your understanding? And maybe the acceptance criteria for the finished product, that you couldn't look at that as a finished product?

DR. FISCHER [In Audience]: Well, I can make a comment in two directions. One is that we as a company submitted a document to the docket, and we referenced some examples there, and you can read from there.

For me, the big question is we have to face this heterogeneity situation. And we worked with a non-glycosylated molecule, retrovase [ph]; developed it. And even though it's not glycosylated, simply from the modifications that we could identify, you would come up to 20,000 or

30,000 potential permutations. And without having an idea where those may come from, and which process step, and how you can control that, I can hardly imagine that you have confidence that you can have a consistent product produced simply by looking at the end product.

So in this context, we deeply evaluated the process and tried to understand at which part in the process temperature, pH, and you name it conditions, can you see chemical modification, and how can you control the process in a way that you limit these modifications? So this is our experience where we used that approach.

DR. CHANG: Well, I just want to make a personal comment on that. I assume the follow-on company also will spend a lot of time to develop

their own processes. It's not saying they will not have a process. They will have a process. It's that their process may not be the same as the innovator's process.

So some of the quality attributes that follow your discussion--that they can also learn from their own process. I think the key issue here is whether or not they can identify the quality attributes that have significance to the safety and efficacy of the product.

DR. FISCHER [In Audience]: Yes, I can agree. But the originator develops this understanding and the data in the context of clinical development and full-blown clinical studies. So that goes together with it. So if you say, "I can control my process, I can understand my specifications, and I tested that material in large-scale clinical trials. I have all these links and elements that give me confidence that this is a safe product and an efficacious product." So looking at the analytical characterization alone to me is an insufficient way to address the

problem.

DR. DILIBERTI: If you have a question, please step up to the microphone.

DR. BENNETT [In Audience]: Yes, I'm Bill Bennett, from Process Development Group at Genentech.

I started there in 1982, and we worked on a couple of projects early on, growth hormone and TPA. And we had problems that were relevant to these points in both those projects. With growth hormone, we had a product on the market, pituitary drive growth hormone, that we were trying to mimic. Our recombinant growth hormone was immunogenic. Over the years, we've never been able to fully explain and scientifically explain the basis for the non-immunogenicity of the pituitary growth hormone or the immunogenicity of our material.

In the case of TPA, we had two methods of manufacture. One was in roller bottles, the other was in suspension cultures using the same cell line. It was a change in the process of manufacturing. We ended up with different

pharmacokinetic properties of those preparations. And we've never been able to come to a complete understanding, even with having spent a lot of time trying to understand the various components of those two TPA preparations--never really understood the basis of the pharmacokinetic differences between those.

And if we can't do that in our own hands with the complete basis of the development of the first product and second, it seems to me very hard to do that by reverse engineering.

DR. DILIBERTI: Excuse me. Can you come back to the microphone? I have a question on the growth hormone example. Did you see batch-to-batch variation in the immunogenicity of your product over time?

DR. BENNETT [In Audience]: That's pretty hard to answer. We did lots of animal studies. We saw differences in immunogenicity with different methods of preparation. But I can't answer the question with respect to batch-to-batch in humans.

DR. DILIBERTI: And then a follow-up to

that is, how do you ensure that batch-to-batch you have the same immunogenic profile, and it's not varying?

DR. BENNETT [In Audience]: Well, the way you do that over time is that you find that your product doesn't really show changes in the percent of patients converting to antibodies over time, which suggests that your batches are relatively consistent over time.

DR. DILIBERTI: So that would be via post-marketing surveillance?

DR. BENNETT [In Audience]: That's what you would have to do. You'd have to do that over time to find that out, yes.

DR. DILIBERTI: Okay.

DR. CHAMBERLAIN [In Audience]: Just a very quick comment from Paul Chamberlain, MDS Pharma Services.

Okay, different products in the human growth hormone class have different degrees of immunogenicity. But what are the clinical sequelae? Can anybody comment?

DR. BENNETT [In Audience]: You want to know if there are any clinical sequelae to the immunogenicity of growth hormone? We didn't get

our initial product approved on schedule because the FDA was very concerned about growth inhibiting antibodies to growth hormone.

DR. CHERNEY: Okay. Just to remind the audience, we would like to focus on the physical chemical attributes of those things; not necessarily on all the clinical sequelae.

But I think one of the things that comes out of the first statement that Charlie makes is that if you say, okay, you have complete chemical characterization; can that predict immunogenicity? Can that actually predict safety and efficacy of the product? How far can you rely on this complete--How complete is complete? And do you know the actual distribution of every molecule?

You've heard about the combitorial thing that Steve Kozlowski was talking about, that we're looking--Most of these techniques will get averages; and yet there's actually a distribution,

heterogeneity. How do those current analytical techniques address that heterogeneity? How do we know that those differences aren't an issue? It's an issue for everybody.

To the microphone, please.

DR. NAKTINIS [In Audience]: Again, Vytautas Naktinis.

I would combine again answers to both questions. But first, I would like to address the comment from my colleague from Roche. So again, we develop our CMC; improve standards. Everyone, it takes years and years of work, a lot of work, so we know our product, we know our process. And therefore, we can correlate, assign--to the same degree, I suppose, innovator--impurities to certain expected effects.

And now let me reverse the table. The favorite argument which comes from innovator industry is that because they know the product, they know profiles, I suppose, and they have clinical data; therefore, they can deduce logically which particular impurity apparently has what

clinical effect.

But let me ask the audience. Is anybody aware that there would be any clinical trial set up to specifically identify effects of [inaudible] isoforms in order to understand what these isoforms are actually doing, or what effect? I, personally, no. And I believe that nobody is designing clinical studies to address impurity issues. Let's be clear here.

DR. HARRIS: Well, if I could respond just briefly, we do a lot of analysis on serum samples now, where we go back and repurify the material and look at the characteristics and say, "Okay, which ones seem to mediate, for example, accelerated clearance?" Those ones will be removed from the population of material. Whereas the ones that tend to retard clearance tend to stay around.

So we actually do quite a bit of analysis so that we can understand the characteristics that mediate clearance, which is one of the easiest ones. But where possible, we use the animal models to look at other effects.

DR. MOORE: There's one example, a specific one, about the deamidated form of human growth hormone that has been looked at in clinical

trials to support the aqueous formulation--aqueous formulations, actually, several companies.

DR. SEAMON [In Audience]: Barry, can I make a comment?

DR. CHERNEY: Sure.

DR. SEAMON [In Audience]: Ken Seamon, Amgen Corporation.

I think we have to come back to one of the most important points, which was brought up just recently. And that is really assuring the safety for patients who are administered these products. So given that, I want to come back to just one or two of the points that were made.

The first is the first point here: A complete comparative characterization is possible, and routine. I would argue--and this is based on our practices at Amgen, as well as previous companies--that certain types of changes, that is true; that when you do make certain incremental

changes to a process, and you understand that process, it is possible to qualify those with analytical and other studies.

However, when changes are made to the fundamental technology--which can include the cell banks, methods for expansion--then your ability to rely on those step-wide changes is somewhat limited. And I would argue that, for example, comparing higher-order structure--that's just one example--maybe 80 percent of your species, but certainly not the lower percentages, it could elicit some type of immunogenicity.

So with regards to a standard for comparative characterization, our approach is that you need to look at the setting. And when you make fundamental changes in the technology, fundamental changes in the processes, as the manufacturer of the reference molecule we will conduct studies to confirm safety and efficacy; again, depending on the setting. And so that is no different standard than should be applied to any molecule that goes into patients.

So now, reflecting back on the value of the database that the innovator has, if you reflect back to the criteria for specifications in ICH,

it's based on your manufacturing history, your stability and, very importantly, what's going on in the clinic.

So I'll reflect back to a comment regarding GCSF that was attributed to Linda Woodle. When additional species were detected, either based on development of new methodologies or process changes, there is an ability to go back to early clinical samples. And the first thing you're going to ask, whether you're an FDA regulator or any type of manufacturer of a product going to patients, you're going to say, "Was this in the patients, in the trials that established the safety and efficacy of this molecule?"

That is one advantage. And again, nobody is arguing that any manufacturer is capable of developing a process for a molecule. What we're talking about, though, is extrapolating back to another molecule and another process safety data.

With regards to complexity, again--and I'm referring back to a comment made by erithroprotein [ph]--I think we have to be a little bit careful about trying to be a little bit too simplistic with regards to product quality attributes. Everybody knows that sialylation and glycosylation are

important for clearance of erithroprotein. However, if one just looks at isoform distribution, you soon recognize that even though products may have a very long half-life in serum, they may have lower affinity to the receptor. So that the overall pharmacodynamic effect of the product is intimately related to the isoform distribution in many ways; which is not easily discernible just by the number of bands.

In addition, if you look at the commercial erithroprotein products that are on the market, you will see that even though they all have a significant amount of sialylation, they all have very different fingerprints that are associated with different pharmacodynamic properties, as well. Thank you.

DR. HARRIS: Can we reopen the question of whether or not people feel that the current analytical technologies are good enough? I have to say that, having been humbled by experience, I don't think they are. And every time that we've introduced a new molecule, we've done detailed characterization and thought we've found everything. And then later, when you apply newer techniques to older proteins, you find that there

are other forms there that you hadn't detected previously.

So at no time in the 21 years that I've been in the field have we had the ability to absolutely characterize proteins. And I'm not convinced that we're there now.

DR. CHERNEY: Is somebody going up?

DR. NAKTINIS [In Audience]: A very simple comment. We should not be speaking about absolute characterization of a protein. That is the "holy grail." So we are speaking about comparative characterization. And we should also remember that there is a limit of isoforms, or minor [ph] forms

or whatever, which is well established through the work of innovators. So as long as we are below the limits of what is known from natural variability batch to batch, or in general between different approved manufacturers, we logically, scientifically, are safe, we are okay.

DR. HARRIS: You're still constrained by the test methods that you selected, though, right? You can't get away from that problem.

DR. NAKTINIS [In Audience]: [Statement Inaudible.]

DR. HARRIS: You're still constrained by the test methods that you've selected.

DR. NAKTINIS [In Audience]: [Statement Inaudible.]

DR. CHERNEY: Speak in the microphone, please. Okay.

MS. SENSABAUGH [In Audience]: Hi. I'm Suzanne Sensabaugh. I work for Sicor, Inc., a subsidiary of Teva Pharmaceuticals.

And I would like to ask the panel a question. And it follows along the same line we're

going, but we're sort of going down a different track. I think everyone in the room is aware of the six products that we have on the market today, the HGH products for immediate release. And we know they're all 191 amino acids. We know what they look like. We know what they feel like. We know how they behave in the body. They've been on the market for over 17 years. They were approved with abbreviated safety studies, with abbreviated efficacy studies. We know immunogenicity is very low, it's rare, it's transient.

But bringing it back to this question--Oh, and also--and this sort of fits into Ken's question--we know the manufacturing process was different for at least five, if not six, of the products. Most of them were bacterial cell derived; one was mammalian cell derived. So very different--Very different manufacturing processes produced the same product.

So getting back to the question about the analytical capabilities today, I mean, the first product was approved back in 1987. And at that

time, FDA determined--You know, we knew what the structure was. And analytical comparability analyses have come so far since that time.

So the question that I would like to ask the panel is: What is there about HGH that you don't know, that you could find out through your analytical techniques?

DR. CHERNEY: Well, the panel's not here to answer the question--

MS. SENSABAUGH [In Audience]: Oh, so can I ask the audience?

DR. CHERNEY: --so I think it's actually the audience that should try to address that question. But before you go, you have all this data. I'd like to see you submit it to the docket, all this data that you have. You know, you can at least summarize and reference the data.

DR. HORA [In Audience]: Maninder Hora, from Chiron.

I wanted to point out two specific instances when the analytical tools would be unable to distinguish between an attribute. For example,

aggregation, it's a composite, it's a distribution. So two aggregation states combined can give you an average number which could be arrived at from many different angles.

So it really isn't that easy to distinguish between--For example, for those of us who use light scattering can tell you that a small amount of large molecular weight molecule could totally skew the distribution.

I think the other thing that is obvious but hasn't been talked about is presence of certain excipients. My colleague from Teva pointed out that they can take a marketed drug and analyze it. Well, some of the excipients could prevent you from actually looking at every aspect of that molecule. Of course, an extreme example of that is human serum albumin. But certain surfactants could change the tertiary or secondary structure of a protein; which may be okay, because it's been tested clinically and pre-clinically by the sponsor. But I think those subtleties would escape someone new. Thank you.

MS. NOVAK [In Audience]: Jeanne Novak, CBR International.

I was hoping to just put out to the panel,

maybe we could get a little bit more clarity about our discussions. And that is the difference between doing characterization of a API and/or a drug substance, and performing comparability. And I feel like the conversation has gotten a little bit mixed, and some of the comments are a little bit mixed, between those two issues.

I don't think anyone, again, would disagree that API, whether it's an innovator product or whether it's a follow-on, does require the fullest characterization that we can provide. I mean, that's our responsibility, and it changes with time and new techniques. But I think one of the issues that gets to be somewhat problematic is, again, what do you do with those results?

And how do you not only compare it, even if you had a best-case scenario where you could compare head-to-head two products, different companies, or different manufacturers--I've heard

someone say "the same." At one level, that might be even with the characteristics. But again, it doesn't necessarily translate to comparability, because comparability, of course, is impacted not just by the characteristics of the API, but, again, as already commented, the milieu in which it exists, the excipients. Also, again, I think you opened the whole session with container closure issues that can change product as well.

But the bottom like is I feel like we sort of have a drifting discussion about characterizing molecules, versus demonstrating comparability of drug substance; which I think are related, but are not in fact the same.

DR. O'CONNOR [In Audience]: John O'Connor, from Genentech.

I think I'm going to do kind of a little bit of a hodge-podge of answers to questions. For example, with the growth hormone, in terms of the process change and what caused immunogenicity, we certainly were studying it, because it was in my lab at the time. And we could find no physical

chemical difference between the preparations; although we did take some great strides in process development and animal studies. So even though the characteristics--by silver stain and by peptide maps, etcetera--were the same, we could not see the difference between the immunogenetic process and the non-immunogenetic process.

One of the things that I think, again, that's critical to this is that the product attributes are very, very important; but they're still probably about 20 percent of the iceberg in Steve Kozlowski's slide that talks about process knowledge. And I think we've touched on this in a number of different ways, but the way that you validate the ranges and the way that you know that the mixtures that you are making are safe is from clinical trial development, so you know that the range that you're making is a safe range.

And the question then becomes, well, what's the difference? How much of a difference would you see? Because undoubtedly, different manufacturers are going to make a different mixture

of things. There's no way to make it identical. So what's a substantial difference, and how do you compare it to what's out there? And the point is that the APIs that we have are not really commercially available. So how do you compare a final product with an API?

And then the last thing is the percent change. In terms of the carbohydrate, we had a 3 percent change in the carbohydrate moiety that wound up with a one year delay to do a clinical trial to demonstrate the safety of that. So again, we've proven the ranges as the innovator. Thank you.

DR. CHERNEY: And the last speaker? And then we have to, I think, move on.

MR. TRAVIS GALLAGHER [In Audience]: Just hoping to move us towards a sense of guidelines, general guidelines, it seems to me that what we might have is a profile for the innovator's product, and then a physical measurement-based profile for the follow-on. And then we would in some mathematical sense take a correlation. And

the higher the correlation of those profiles, then the less we would feel we needed to pursue clinical tests.

But of course, there would always be some of those necessary; but there would be a sort of a sense that the better the correlation, then the more we would be confident that we could follow the original findings for that molecule. All of this would be weighted by the complexity. So that for large proteins, we would be more doubtful and require further evaluation.

DR. CHERNEY: Okay, thank you. I don't know if we've resolved anything, but we'll move on to the third question, which is: What are the appropriate standards for the characterization of identified attributes?

And I think we've started already hitting upon them. I think one of them is: What is the nature of the comparators, and what are the issues surrounding that? The second part of this question, really, is: How do you establish differences between the comparators? And then

thirdly is: How do you evaluate those differences and acceptance criteria?

And I think we've already started touching on these issues. But first, we'll turn to Reed.

DR. HARRIS: Thanks, Barry. Yes, so that really is the key question that was asked by the audience. It is: How do you apply comparability concepts if you are the follow-on manufacturer and you don't have access to the historical data set?

You know, we do a lot of comparability programs, and we know that we can make incremental changes because we have samples that go back all the way to the phase three clinical program and so we can demonstrate that we're staying within an appropriate range of characteristics.

And it's not clear to me how someone could go to the pharmacy and come home with vials and potentially reprocess them if there are other intermediates that need to be taken out, like carrier proteins; and then somehow make a claim that they can do comparability by taking, again, pharmacy-derived samples and comparing them to

their own production.

The other question up there is: How do you link the follow-on lots to the innovator's clinical material without the common reference? You know, there are some standards for certain proteins. Those are generally activity standards. They're not appropriate for use as purity standards. So how does the follow-on manufacturer then claim that they are making the same protein?

And similarly, they are restricted in that they don't have the same methods and they don't have the same reagents that are needed to run some of those methods. And we heard earlier the opportunities to rely on what is in the public domain or in the literature. But bear in mind that those are rarely the current protocols. What you're looking at is what somebody did perhaps five or ten years ago, and the innovators are continuously updating their methods, as well.

Another question that's up there is: To what extent does the follow-on biologics manufacturer have to recharacterize and reassign

impurities? And we spend a lot of time looking at minor peaks and trying to define them as impurities or not. Does that work have to be repeated? And how would you repeat, for example, the potency testing that is critical to defining impurities if you have a different method? And how would a product reviewer then be able to judge whether they are measuring the same impurities and applying the right test?

And then, the last question is a little bit harder, because most of what's known about the safety of a molecule comes from the innovator's experience. And the follow-on biologics manufacturer then has to turn in an application that has identified the critical quality attributes that the innovator had generated. How is a product reviewer going to be able to evaluate whether or not the follow-on biologics manufacturer has picked the right quality attributes, without either deliberately or inadvertently making reference to the innovator's proprietary know-how in that regard?

DR. DILIBERTI: Thank you, Reed. I believe in most cases, although you may have a few instances where there is a publicly available

reference material or in a few cases also a monograph, in most cases the appropriate comparator would be the brand product itself.

And then, when we turn to acceptance criteria--how close is close enough?--again, there might be a variety of means by which to determine the acceptance criteria; but a large part of that is going to be determined based on the variability of the brand product itself.

DR. CHERNEY: Now I'd like to turn it over to audience discussion. And perhaps maybe we can talk about just the comparator. We've heard that perhaps the drug product is the most appropriate comparator, but we also heard in an earlier discussion that sometimes excipients prevent that. If you have HSA in the thing, if you have some other--other excipients can interfere with that analysis. And it requires, in fact, processing to remove that.

You have also complex proteins like polyethylene glyco-oxylated proteins whose pig moieties make it almost impossible to look at the drug substance in the presence of the pig; so you have to process that drug product to yield a drug substance that is characterizable. So what are

those issues?

DR. TOWNS [In Audience]: John Towns, from Eli Lilly.

As we've made manufacturing changes, I think the framework has to start kind of low-complexity, moving up. So this is for insulin and human growth hormone. As we've made manufacturing changes, it's been a requirement by the FDA in our comparability protocols that we have no new impurities. And because we have tests that can get down to the part-per-million, really, we're talking identical.

So I am suggesting then for low-complexity proteins that the standard is identical, because that's what I'm being held to now. If it's not, please let me know. Give me a call. Because then

I can rip out some columns, I can use some lower-grade raw materials, and have this be a level playing field.

DR. DILIBERTI: Are those process-related impurities, or product-related impurities that you're talking about? I'm referring to those that you have to monitor to the one-ppm level.

DR. TOWNS [In Audience]: Yes, in this case, for what we had they were product-related. The in-process-related impurities were expected to be--you know, that we have like Cocel [ph], that would be our process-specific assays that we needed to provide.

DR. CHERNEY: And of course, if you had new product-related impurities, you could have always gone to a higher level of testing to perhaps evaluate those impurities, right? But in order to get approval, you're saying for those things, without any additional testing, you would have to have the same purities, right?

DR. TOWNS [In Audience]: Yes. The expectations per the 1996 comparability guideline

would be that if you didn't show comparability at the physical chemical, you would move on to the next level. What I'm saying is "comparable" is not the word.

DR. CHERNEY: Right.

DR. TOWNS [In Audience]: It's "identical."

DR. CHANG: Yes, to add on to that, it is that, John, you did mention you used the comparability protocols. So that we do not encourage the company to use comparability protocols if we find that the clinical study was deemed necessary. So it doesn't necessarily mean that you cannot, like Barry mentioned, use the clinical study to justify some of the impurities. But you are right, the comparability protocol may not be suitable.

DR. CHERNEY: Right.

DR. MARSHALL [In Audience]: Michael Marshall, from Novo Nordisk.

When we carry out comparability exercises on second-generation manufacturing processes for

insulin, we use data from a number of batches; usually, three of the drug substances from a new process. And we compare both historical data from the current process and generally three recently consecutive batches of drug substance from a current process.

And my question to the follow-on manufacturer would be, yes, we can accept, of course, that they can buy our product from the pharmacy in the product formulation form; how can they ensure that the product they buy--They can buy different batches of that product, but how can they ensure that there are at least three batches of drug substance represented in their comparative products? To me, this is a logistic problem. I don't see how they can ensure that.

DR. CHERNEY: Any responses to that question?

And of course, a little bit other added factor is, the stability of that molecule has an expiration date. And so, you know, what are you comparing when you're comparing a product that is

on the shelf, versus a product that is at time zero?

So there are other things. And how do you set the acceptance criteria when you realize you're not looking at the release data, but you're looking at stability data, and all the things that you're comparing, you're comparing stability samples to drug product at release? So the comparators, when you do compare drug product to drug product, there are other issues that fall in out of that. And let's speak to some of these issues.

I still haven't heard whether you can compare things that are in HSA, or there are things to do? Or how do you handle excipients? What's the approach where you can't do a comparability or a similarity exercise?

DR. HORA [In Audience]: This is Maninder Hora, from Chiron, again.

Obviously, I'm not going to answer that question, because I asked that question.

[Laughter.]

DR. HORA [In Audience]: But, you know,

the "A-B-C" of specification setting is it's based on process and product experience, stability testing, pre-clinical and clinical experience. And that whole knowledge goes into specification setting. And just taking a few lots of the drug product from the pharmacy--and we've pointed out some of the limitations--I just cannot see how we'll have specifications which are relevant and safe and effective for the drug product in question.

DR. BADER [In Audience]: Fred Bader, from Global Biologic Supply Chain of J&J.

I guess the first question you just asked, I mean, one of the things is if you're trying to compare a final dosage form against a product that already has HSA or some of the detergents in it, it's very difficult to be able to do that sort of thing without doing enough perturbation around the product. I mean, you really don't know what you're looking at any more. So I think that's a fairly weak thing.

I think the comment I wanted to make on

this whole thing is we talk about characteristics of the proteins. We believe that we understand what those really mean. And the reality of life is the way this works is we develop a process to make a protein that we want to make. Then, if we think we've got something that looks pretty good, then we basically characterize that and set specifications around it. And if we can run that process over and over and over again and always create a molecule that fits within some set of constraints of those specifications, then we say we have a consistent product.

Then we take that consistent product--We have no idea if that's safe or efficacious or anything. We take it to the clinic to determine whether it really is a safe and efficacious, non-immunogenic, etcetera, kind of product. In reality, we don't have any idea of how those specifications really relate to the safety, efficacy, immunogenicity of the product. Is 2 percent aggregate too much? Is it 10 percent that doesn't make any difference? Is 0.1 percent? We

don't know. We set an aggregation spec sort of by pulling a number out of the air, sort of based on statistics, generally with negotiation with the regulators. Those are the kinds of things we go through to try to set up a meaningful set of specs, mostly to make sure that we stay within the process range.

Then if we, ourselves, as an innovator, were going to make a change--And we've looked at these things. We've developed new cell lines, for example, for products, etcetera. If we were going to put those into the marketplace internally, without any support or help from the regulators, we come to the same decision: that we would not make that kind of a change, even though it fit all of the specifications and characterizations, without taking that product into some kind of clinical study. Because there are just so many things that we don't know and understand.

If you change a cell line, you may be picking up some kind of protein from the cells themselves that could be causing a problem. If you

change the cell line, you probably change the media along with it. You may have changed some other things in some minor ways, or whatever, that could change the product. And so you really have to go in and do something.

Now, that doesn't mean you have to do ten years worth of clinical studies; but there are a reasonable number of studies, PK studies, PD studies, as were discussed this morning. For a lot of the proteins, immunogenicity studies are not that hard, because the levels of immunogenicity are up around 5, 10, 15, 20 percent. So it doesn't take that many patients to see if your immunogenicity level is comparable to the original products on the market.

MR. POLASTRI [In Audience]: This is Gian Polastri, of Process Development, Genentech, again.

Because I've been doing process development a long time, I have a question to add to what was said previously. When the innovator is contemplating introducing some of these incremental manufacturing changes that have been alluded to,

the appropriate standards that we are called to compare all those changes to begin only with the final product.

It has been discussed previously, also, those comparability exercises also have to match comparability of the drug substance. In addition to that, we also have to match the performance attributes of the manufacturing process. All of which are designed to relate whatever the impact of the manufacturing changes would have to the way the process was originally done in support of the pivotal phase three trials.

So any process steps that have been altered, have been changed as a result of the amendments, have to be revalidated to ensure that they still perform the same function as they did back when we submitted the original filing for licensure.

I'm not sure how you can--Or let me ask the question this way: What information would we need to know about a molecule that's been out on the market, that would allow us to let all of that

other database fall away as an integral part of our standards?

DR. CHERNEY: I was looking for somebody to respond to that.

DR. SCHIESTL [In Audience]: Martin Schiestl, from Sandoz.

I want just to comment, or to make a statement on the comment of Dr. Cherney, because of how a protein producer can deal with excipients of the innovator drug product. Normally, you start with characterization of the innovator drug product. So we use this material for development of the analytical methods using all those orthogonal, analytical techniques.

And also, to deal with this excipient question, in the way that we just prepare those formulations and validate the analytical methods with respect to those excipients--For example, HSA can be very well separated by a number of chromatographic methods. And this can be very clearly validated and also shown by data if it works or not. So this has to be addressed, and I

think it's possible to address.

And I want also to comment that a follow-on protein process stands on its own stand-alone drug product and drug substance process development. So we have all those data required for additional comparability study in place; so we have all that process knowledge in place; for the full drug product development, for the full drug substance development.

And maybe also a comment on the statement of Dr. Moore. Because those critical product-related impurities and substances, those substances you have mentioned like oxidation, deamidation, truncation, can be very well synthesized, prepared in model experiments and stress stabilities. And so, also, those methods can be validated according to this.

And a last comment. A lesson that we have learned, also, for the small molecule businesses, that the target should be that a follow-on development must be able to characterize product better than the innovator, so that we are able to

design the process to the profile of the innovator product which is on the market.

DR. CHERNEY: Yes, I would just like to comment, I guess, and ask you a question. When you have a [inaudible] there you're actually doing a process now on a kind of product to get rid of it. How do you know you don't alter the active ingredient? How do you get 100 percent recovery? You lose things. You might alter things.

And it sort of refers back to Reed's second question. In the absence of a common reference, how do you assure that the data you're generating from the comparison is totally relevant to the actual drug product that is being marketed currently? Because you've entered into things, you're doing things that there's no reference back to now.

I think I would feel more comfortable if I had a reference to say, "Okay, this is actually going to look like the innovator product, from what I know of the innovator, or what we all agreed is the innovator. This is the product. This looks

like it." But without that reference, is there a risk to it? And how do we mitigate that? How do we make sure that the things that you're seeing are actually what the innovator has seen and confirms?

DR. SCHIESTL [In Audience]: Maybe, to your first question, those topics have to be addressed. I don't say it is in all cases possible. I think it's possible in most cases. It can be then demonstrated by data.

If it is not 100 percent possible, then a worst-case scenario has to be--For example, if aggregation is not possible to evaluate the final product, then the limits of aggregation in the follow-on product have to be really as low or nearly at zero.

And the second is that the missing standards--Physical chemical characterization is only one step of making a full comparison. For example, certain issues like immunogenicity cannot be predicted by 100 percent. So in this case, also, a safety and efficacy study is required to build up its own scientific standard.

DR. CHERNEY: Well, just take an example. If you have aggregates, and say the innovator has shown the FDA that they have a 5 percent level--or

a 10 percent level of aggregates, and we have clinical data to support that. And then the other manufacturer comes in, or the follow-on comes in and says, "Well, we only have 2 percent aggregates, and that's all the innovator has, too." How do we interpret that information?

If we were comparing them, we'd say, "Something is going on here." One is reading something very different than this. And how reliable is that comparative data? One questions then the accuracy, or the precision of the assays, or accuracy of the assays that are being used.

And we know, for example, analytical ultra cenobrogation [ph]. Wherever you set that meniscus, you'll get a different aggregate number, just based on that method. And so, using the same two samples, you'll get very different methods, because the accuracies of the assays are different. And so, you know, it does enter problems--

DR. SCHIESTL [In Audience]: Yes.

DR. CHERNEY: --in interpretation, without a reference standard.

DR. SCHIESTL [In Audience]: You can compare only when you use the same methods. So if you are using different methods, then the

comparison is lacking. Yes. Each method of aggregation, though, delivers a different result. So you have just to address all types of aggregates--soluble, insoluble; small aggregates, large aggregates. And you have to set up these aggregation analytics to cover all those principles and those criteria. You will get different results.

But after all the whole picture, the databases should be sufficient to make a clear comparison. And the small portion in the comparability exercise which is missing there, it is then the task of the clinical studies to be confirmed.

DR. HARRIS: If I can ask a follow-on question, the assertion that a follow-on

manufacturer would use better analytical techniques to characterize the molecule, versus the innovator, what is that based on? How would you ever know what the innovator's techniques were?

DR. SCHIESTL [In Audience]: In the analytical field, the state-of-the-art methods are very nicely described and published. And we have heard, also, from the September workshop a lot of horror stories where we see this can be just based on maybe not using up-to-date, state-of-the-art analytical methods.

So we touch and challenge the state-of-the-art within the scientific community with protein analytical experts and protein analytics--Yes, and just convince ourselves by data. So this is the target we have in the development plans. And if we see, okay, we can reach this target, and if we can get the data in pretty good shape, we can move on to the clinical studies, and so on.

DR. CHERNEY: Okay. Thank you.

DR. KARUNATILAKE [In Audience]: Chulani

Karunatilake, from Chiron.

If I may, I would like to shift the discussion from aggregates to succinylmide [ph] intermediate, or the cyclicamid [ph], as it's commonly known. I think, just like aggregation, that's one of the most difficult variants to characterize. As I think somebody already pointed out, the main mode of detection for the cyclic intermediate is usually proprietary analytical separation techniques--exchange most of the cases and some of the techniques.

And the reason that detection and characterization of cyclic intermediate is especially difficult is because it's of an unstable nature. It can easily open up, the cyclic intermediate can open up and go to the end product. As well as the mass spec characterization is not particularly amenable to cyclicamid detection because the mass spec conditions themselves can alter the pattern.

And as I said before, the way the innovator detects the cyclicamid intermediate

typically is a proprietary analytical technology that is not available to the follow-on biologics company. And again, I think Reed pointed this out, there are several examples now in the literature, in my experience, where the cyclicamid can directly influence the biological activity. Potency, for example.

DR. SUBRAMANIAN [In Audience]: Veerappan Subramanian, from Barr Pharmaceuticals, Kali Laboratories.

I listened to the seminar this morning, and was very happy to see what was said on the podium. There appeared to be a lot of progress being made with the follow-on biologicals area. Rather than call it "generic biologicals," I would stick with the politically correct terminology of "follow-on biologicals."

The gentleman from MIT, the professor from MIT, spoke. He gave a nice speech about what techniques are available, how they can characterize them, and so forth. People from both sides of the aisle, as well as the FDA, made a lot of good

speeches. Janet was so excited she came over and said within a few months she'll release a position paper and following that, at some point in time, she'll put out a guidance.

Sitting through this meeting this afternoon through this distinguished panel here, I've found it very disturbing. I think even though I come from the follow-on side of the industry, I just want to take my hat off for a moment--I would like all of you to take your hats off. Rather than be Amgen and Genentech and whoever you are, think about that we've got three million people out there in the marketplace, out there in the society, which the FDA today represents. I guess they will represent them. Twenty years ago, I believe that some of the simpler molecules of this kind were approved, and they came to the market. Twenty years later, so much more knowledge, so much science has advanced, so many new techniques have become available.

And somebody said--I think somebody from Amgen or somebody said that, "My product in ten

years has not changed." If your products in ten years have not changed, and so much technology has become available to me to characterize those, why can't the people take advantage of that today to characterize?

And in my own 20-some years experience in the multi-source product area, I've seen when you try to put together a equivalent product--in this case, a follow-on product--we are more handicapped due to the new technology available to us. We can do a better product, better merchandise than what is available in the market. So we struggle wanting to make it equivalent; which is what you do all the time. That's what we're faced with.

The gentleman from Teva earlier said that we also spent years and years struggling to develop a product, struggling to characterize a reference product, which is what we do to these products as we learn. And after all the learning, there has to be at some point some way to use a known standard combining all the physical techniques available to us, combining some kind of PK/PD work, combining

some kind of limited clinical work available.

As the gentleman earlier was saying about when they have cell line changes of whatever they do, they go do limited clinical studies. Why could not a follow-on generator do the same thing, and get into the market? Why do we have to be so everybody seems to be wanting to protect their territory, protect their proprietary information?

Much information is available in the public domain, much information is available in the scientific community. We use that information available to us, even though we do not have the same information that Amgen and Genentech and Chiron have in their files. You are struggling through the same struggle that we will be struggling through. And at some point in time, the agency should be able to define a standard, we should be able to go forward, and we all should be happy.

DR. HARRIS: If I could just speak as an individual for a moment, and say that one of the concerns that I have is that a follow-on

manufacturer, their product will generate a new safety issue, and it will fall back to the innovator to prove that they don't have the same problem.

And the easy example for that is Amgen having to defend itself with respect to the ritzelplasia [ph]. So I mean, there is a risk in our business, as well, when someone else generates a follow-on product and claims that it's equivalent to ours.

DR. CHANG: Well, moderator, excuse me. Let's not spend a lot of time on opinions. We said that we are going to discuss scientific issues.

Now, before you sit down, can I ask you a question?

DR. SUBRAMANIAN [In Audience]: Yes.

DR. CHANG: What information can you learn on molecular attributes that related to the safety or efficacy issues? Can you give us one example of molecular attributes that actually related to safety issues, that you can learn from the literature or any studies that you performed?

DR. SUBRAMANIAN [In Audience]: I'm not enough of an expert to be able to comment on that question, sir. I would defer to the experts to

that specific area. I'm just listening to the science as it develops, listening to what is being said. And I'm coming from--I'm a paper-pusher. I'm president of a company. I do not know the specifics of what's being discussed.

DR. BENNETT [In Audience]: Could I share one more example? Bill Bennett from Genentech. I was involved in the development of a product called "Somovert" [ph]. It's a pegylated [ph] growth hormone variant. Now, based on the sales of that product, I can't think of why anybody might want to copy it--

[Laughter.]

DR. BENNETT [In Audience]: --but just as an example, the way we had to do the host cell protein assays on that product was on the pre-pegylated bulk. Because once the product was pegylated, the impurities were also pegylated, and no host cell protein assay was capable of picking

up those impurities in the final product. So even though we did have a host cell protein number on our C of A, that test was done much earlier in the process. It's very hard for me to imagine how that could be reverse engineered.

DR. CHERNEY: Thank you. Well, one last question. I think we're at the end of our time, but one last response.

DR. NAKTINIS [In Audience]: Vytautas Naktinis again. Hello.

So I think we're again putting our discussion into black box, a lot of things. Let's be more science based, and go step by step, from low complexity, as this conference actually tries to do. So low-complexity proteins. Look, we have compendium articles. And in Europe at least we have chemical reference substances. Guess where they're coming from? They're API, from the innovator. So that's one. But again, case by case, please remember.

So simple answer, already my colleague from Sandoz very well responded: What do you do

with excipients? If you cannot remove excipients--of course, you do that through validated procedures--you add excipients to your material, at the very least, in numerous approaches, and you analyze.

But I would like to go to the second question of Dr. Harris on the slide, if possible. So how do we relate our material, follow-on material, to the innovator's clinical material? It's so simple. We don't need access to clinical material you used in your clinical trials. We have your commercial batches. And if you now tell that commercial batches are not, let's say, reflective of your clinical batches, I will be very much surprised. So therefore, if I have your commercial batches, it means I have access to your clinical batches quality attributes. Simple.

But a lot of questions were asked to the follow-on manufacturers here today. I have no time, unfortunately, to answer; but answers are available.

DR. CHERNEY: When you come back for the

next session.

DR. FISCHER [In Audience]: Okay. Stephan Fischer, from Roche.

I don't talk from my hat, actually; I speak coming from this industry and having experience in this field. And what do we talk about here? We talk about potential shortcuts. And we try to understand: Can we make shortcuts in the development of a protein by having the uncertainty that's intrinsic to this kind of business?

And this is a discussion we have within the company with our colleagues all the time. But we say we have to be very careful and conscious about the risks that are associated with these kinds of products. And we put patients at risk if we don't do that carefully.

So it's not that we block or that we want to deny that you can develop follow-on proteins. The question is: Can we make significant shortcuts on alternate development? That's the question. If you make a full assessment of your process, you do

your validation, you create a database, you do full-blown safety, efficacy trial, you're there where you want to be. No question. We talk about shortcuts, and the risks associated with that.

DR. CHERNEY: Okay. Suzie, and then that's it. Yes.

DR. MOORE: This session is about physical chemical characterization. You're talking about shortcuts in that area? I thought the question actually spoke to shortcuts of clinical trials, or less patients in clinical trials. That should be made very clear. We're not shortcutting physical chemical characterization--Unless I was mistaken when I heard that.

DR. CHERNEY: No, he was talking about clinical trials.

MS. SENSABAUGH [In Audience]: Thank you, Steve. You provided me with a very good seque into my comment. And I'd like to address the last comment. I'm Suzanne Sensabaugh, here from Sicor, a subsidiary of Teva.

And we've been manufacturing biotech

products for at least 15 years, and we've been distributing those products in 17 countries. On one of our protein products we have given over nine million doses, so we have vast experience with biotech products.

Now, it just happens, in most of those markets we're not the first product on the market, so we're considered a biogeneric. But we're still a biotech product. I mean, that's what we manufacture. The only difference is that we do abbreviated animal studies and we do abbreviated clinical trial programs.

We do de novo product development. We monitor our quality attributes. We characterize our cell banks. We validate our manufacturing process; we validate our equipment; we validate our systems; we validate our facility. And we have full testing specifications, and we have our own specifications.

So the point that I wanted to make regarding the last bullet is that we monitor our critical quality attributes in the same manner as a

brand manufacturer, because we are biotech products and we do that in the same manner. The only thing that we abbreviate--and this gets to Steve's comment--is that we abbreviate animal studies and that we abbreviate our given clinical studies. We do not abbreviate quality, and we do not abbreviate our development process.

DR. CHERNEY: Okay. And with that, I think we're going to have to close this session. But I want to remind everybody that we have another session in a half-hour. And I think we didn't hit on all of the topics, and I think there's a lot of interesting areas to still talk about and get further clarification on. Thank you very much.

And please, if you spoke, please come over and drop your business card off, so that people know. Thank you very much.

[Whereupon, at 3:08 p.m., the session concluded.]

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